

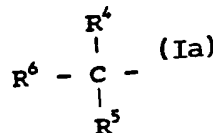
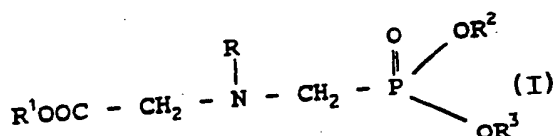


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(54) Title: PROCESS FOR THE PREPARATION OF N-PHOSPHONOMETHYLGLYCINE		



(57) Abstract

A process for the preparation of N-phosphonomethylglycine is disclosed which comprises preparing an N-alkyl-N-phosphonomethylglycine or its ester represented by formula (I), wherein R is an alkyl group represented by formula (Ia) and R¹ and R³ are independently selected from the group consisting of hydrogen and alkyl having one to about four carbon atoms, and R⁴, R⁵ and R⁶ are independently selected from substituted and unsubstituted alkyl groups having from about six carbon atoms wherein any substitution on the alkyl group has electron withdrawing properties, and hydrogens, provided that R⁴, R⁵ and R⁶ cannot all be hydrogen; and thereafter treating the N-alkyl-N-phosphonomethylglycine with an acid, other than a hydrohalic acid, having a pK_a value below about +3 in the presence of an organic acid to provide N-phosphonomethylglycine.

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PROCESS FOR THE PREPARATION OF N-PHOSPHONOMETHYLGLYCINE
BACKGROUND OF THE INVENTION

This invention relates to a process for the preparation of N-phosphonomethylglycine or its esters, and more particularly to the preparation of N-phosphonomethylglycine from N-substituted glycine derivatives.

N-Phosphonomethylglycine, known by its common name of glyphosate, is widely used around the world as a broad-spectrum herbicide to control the growth of many plant species. Generally, it is used in an aqueous solution as one of its salts for application to plants to control the growth of woody plants, aquatic species, grasses, and the like. It is known to be generally non-toxic to humans and other mammals, and environmentally safe. Millions of liters of the formulated product are sold each year for such purposes.

It is known that N-benzyl-N-phosphonomethylglycine (or its esters) undergoes hydrohalic acid debenzylation to yield benzyl halide and N-phosphonomethylglycine or its esters (see for example British Patent No 1 436 843). A large excess of very concentrated (eg 48%) hydrohalic acid is required, however, amounting to many moles of acid for each mole of starting compound. This renders the processing and isolation of the desired glycine derivative difficult, mainly because of the problem of removing this large amount of hydrohalic acid after the reaction.

Attempts to improve the process by the use of starting compounds having other substituents than benzyl on the nitrogen atom, eg to use N-alkyl-N-phosphonomethylglycines, have been attended with the same processing disadvantage (see for example US Patent No 3 927 080). The literature contains no suggestions as to the use of acids other than the hydrohalic acids to remove the alkyl group from N-alkyl-

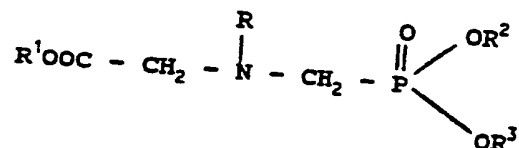
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N-phosphonomethylglycine to produce the desired end product. Now, there is provided an easy procedure to dealkylate a wide variety of N-alkyl-N-phosphonomethylglycines to provide N-phosphonomethylglycine in high yields at an economical cost.

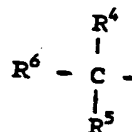
SUMMARY OF THE INVENTION

These and other advantages are achieved by a process for the preparation of N-phosphonomethylglycine which comprises:

preparing an N-alkyl-N-phosphonomethylglycine or its ester represented by the formula



wherein R is an alkyl group represented by the formula



and R¹, R² and R³ are independently selected from the group consisting of hydrogen and alkyl having one to about four carbon atoms, and R⁴, R⁵ and R⁶ are independently selected from substituted and unsubstituted alkyl groups having from one to about six carbon atoms wherein any substitution on the alkyl group has electron withdrawing properties, and hydrogen, provided that R⁴, R⁵ and R⁶ cannot all be hydrogen; and thereafter

treating the N-alkyl-N-phosphonomethylglycine with an acid, other than a hydrohalic acid, having a pK_a value below about +3 in the presence of an organic acid to provide N-phosphonomethylglycine.

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DETAILED DESCRIPTION OF THE INVENTION

We have found that, apart from known processes using hydrohalic acids, certain N-alkyl-N-phosphonomethylglycines, and their esters, in which the N-alkyl substituent is suitably chosen, can be dealkylated by treatment not only with a hydrohalic acid but with any acid whose pK_a value is below +3. Preferably, the acid used is selected from the group that consists of sulfuric acid, p-toluene sulfonic acid, methylsulfonic acid (subgroup A) and trichloroacetic acid, phosphoric acid and phosphorous acid (subgroup B). The acids of subgroup A are preferred, and sulfuric acid is especially preferred.

In the case of sulfuric acid, an adequate molar proportion is less than about 10%, based on the moles of alkyl substituted glycine derivative used in the process. Of the other acids named, molar proportions of about 5% to about 50% can be used, the preferred range being 10% to 20%, based on the moles of alkyl substituted glycine derivative used.

Any number of organic acids known to those skilled in the art can be used in the treatment of the N-alkyl-N-phosphonomethylglycine with the acid having a pK_a value of less than about +3. It is only necessary that the organic acid is water soluble, and lower molecular weight organic acids are preferred. Suitable organic acids include formic acid, acetic acid, propionic acid, butanoic acid, and the like, for use in the reaction medium. Acetic acid is preferred.

The temperatures to be used in the present process can vary within wide ranges. Temperatures between about 20°C and about 100°C provide satisfactory results. Lower temperatures can be used, but the reaction is somewhat slow. Temperatures above 100°C can be used, but as will occur to

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those skilled in the art, the reaction vessel may have to be pressurized at such higher temperatures. Temperatures between about 40°C and 100°C are preferred. When sulfuric acid is used, dealkylation begins at a temperature of about 50°C, and becomes rapid at about 80°C, with copious evolution of the relevant alkene.

In a preferred embodiment of the process of the invention the dealkylation is carried out in the presence of acetic acid as a solvent. This has been shown to impart economies to the process, since the target compound crystallizes directly from the acetic acid in the course of the dealkylation reaction.

In another preferred embodiment, which can be combined with any of the embodiments described above, the process of the invention comprises preparing the alkyl derivative in a manner known per se, and thereafter dealkylating it according to the invention as set out above, without previous isolation, in a one-pot procedure. More specifically, in the preferred embodiment, the N-alkyl-N-phosphonomethylglycine or ester used is synthesized from ethyl chloroacetate and an appropriate alkylamine, followed by ester hydrolysis, followed by phosphonomethylation of the resulting N-alkyl glycine or ester, and that entire process is performed without isolation or purification of any intermediate. In the preferred embodiment N-t-butyl-N-phosphonomethylglycine may be prepared by phosphonomethylation of N-t-butylglycine which in turn may be the product of the coupling of t-butylamine and ethyl chloroacetate, followed by ester hydrolysis.

When the most preferred glycine derivative, namely N-t-butyl-N-phosphonomethylglycine, is dealkylated in accordance with the invention, especially when acetic acid is used as a solvent, iso-butylene is evolved. If, however, there is a

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significant amount of water present in the reaction mixture, then in addition to iso-butylene, t-butanol is obtained as a by-product. As will occur to those skilled in the art, corresponding products are obtained when other glycine derivative are used.

As previously stated, the dealkylation of N-t-butyl-N-phosphonomethylglycine proceeds more rapidly in acetic acid than it does in water; however, it is the high yield of N-phosphonomethylglycine from the acetic acid medium, with minimal processing, that provides a major technical advantage in the process of the invention.

A final product of purity exceeding 90% by weight is obtainable by the process of the invention in a routinely reproducible manner. Typical reaction times are 2 to 4 hours. With cooling and filtration over 90% yields are obtainable.

The following examples serve further to illustrate the invention:

Example I

N-t-Butyl-N-phosphonomethylglycine (100 g, 96% pure, 0.426 mol) was mixed with acetic acid (500 ml) and 97% sulfuric acid (4.0 g, 0.04 mol). On heating the mixture to 50°C in a round-bottomed flask fitted with a Liebig condenser, iso-butylene was detected downstream of the condenser. At 80°C large quantities of iso-butylene were evolved and the rate of evolution of this off-gas increased with temperature. After 3 hours at 100°C there was no N-t-butyl-N-phosphonomethylglycine detectable by HPLC in the reaction vessel, and large quantities of crystalline N-phosphonomethylglycine were present. Cooling to ambient, filtering and drying gave N-phosphonomethylglycine (69.0 g, 95% pure, 91.2% yield). Analysis of the mother liquor

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showed a further 3.7 g of N-phosphonomethylglycine, giving a total chemical yield for this dealkylation of 96.3%.

Example II

5 N-t-Butyl-N-phosphonomethylglycine (100 g, 96% pure, 0.42 mol) was mixed with acetic acid (500 mls) and p-toluene sulfonic acid (14.6 g, 0.085 mol). Heating at 100°C for 4 hours completed the reaction and the chemical yield of the dealkylation was 94%.

Example III

10 Ethyl chloroacetate (122.5 g 1.0 mole) was reacted with excess t-butylamine in trichloromethane and the ethyl glycinate separated from the t-butylamine hydrochloride. The ethyl glycinate was hydrolyzed with hydrochloric acid and the N-t-butyl-N-phosphonomethylglycine (167.6 g as
15 determined by HPLC) was reacted with sulfuric acid (3.8 mls, 0.07 mol) at ambient temperature and the mixture was then heated at 100°C for 4 hours. Cooling to 20°C, filtering and drying gave N-phosphonomethylglycine (118.5 g, 95.8% purity, 90.3% yield). The overall yield from ethyl
20 chloroacetate was 67.2%.

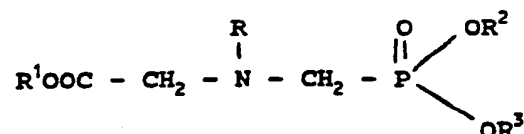
The invention is not limited by or to the details of the specific embodiments described, many of which can undergo wide variation without departing from the scope of the invention.

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WHAT IS CLAIMED IS:

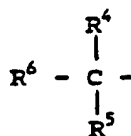
1. A process for the preparation of N-phosphonomethylglycine which comprises:

5 preparing an N-alkyl-N-phosphonomethylglycine or its ester represented by the formula



wherein R is an alkyl group represented by the formula

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and R¹, R² and R³ are independently selected from the group consisting of hydrogen and alkyl having one to about four carbon atoms, and R⁴, R⁵ and R⁶ are independently selected from substituted and unsubstituted alkyl groups having from one to about six carbon atoms wherein any substitution on the alkyl group has electron withdrawing properties, and hydrogen, provided that R⁴, R⁵ and R⁶ cannot all be hydrogen; and thereafter

25 treating the N-alkyl-N-phosphonomethylglycine with an acid, other than a hydrohalic acid, having a pK_a value below about +3 in the presence of an organic acid to provide N-phosphonomethylglycine.

2. The process of Claim 1 wherein R is isopropyl or t-butyl.

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3. The process of Claim 1 wherein R is t-butyl.

4. The process of Claim 1 wherein the acid having a pK_a value below about +3 is selected from the group consisting of p-toluene sulfonic acid, methyl sulfonic acid, sulfuric acid, trichloroacetic acid, phosphoric acid and phosphorous acid.

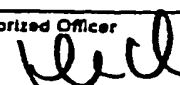
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5. The process of Claim 4 wherein the acid is sulfuric acid.
6. The process of Claim 1 wherein the organic acid is acetic acid.
- 5 7. The process of Claim 1 wherein the N-alkyl-phosphonomethylglycine is synthesized by reacting ethyl chloroacetate with an alkylamine, followed by ester hydrolysis, followed by phosphonomethylation of the resulting N-alkyl glycine.
- 10 8. The process of Claim 7 wherein the alkylamine is t-butylamine.
9. N-Phosphonomethylglycine produced by any of the processes in claims 1-8.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 89/05711

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) * *According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : C 07 F 9/38		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System ¹	Classification Symbols	
IPC ⁵	C 07 F 9/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 3927080 (VAN R. GAERTNER) 16 December 1975, see the whole document (cited in the application) --	1-9
Y	US, A, 4650613 (M.J. PULWER) 17 March 1987, see the whole document -----	1-9
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 26th March 1990		Date of Mailing of this International Search Report 24.04.90
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer  F.W. HECK

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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 8905711
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3927080	16-12-75	None	
US-A- 4650613	17-03-87	None	

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

Concise Explanation of Relevance for EP-A-0297369

EP-A-0297369 was cited in a Supplemental European Search Report for a counterpart foreign application. The reference describes a process for the preparation of glyphosate through a combined dehydrogenation and hydrogenation of N-benzyl-N-phosphonomethylaminoethanol at a relatively low pressure. The process comprises reacting a N-benzyl-N-phosphonomethylaminoethanol derivative in a closed reaction vessel in the presence of a dehydrogenation catalyst and a hydrogenation catalyst with an alkali metal hydroxide or alkaline earth metal hydroxide in water. After the reaction has ended, a mineral acid to liberate glyphosate from its salt.

